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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,911	10/23/2006	Hyae Gyeong Cheon	DE1698PCT	6523

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EXAMINER	
COUGHLIN, MATTHEW P	
ART UNIT	PAPER NUMBER
4131	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,911	CHEON ET AL.	
	Examiner	Art Unit	
	Matthew P. Coughlin	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-13 are pending in the application.

Priority

This application is a 35 U.S.C. 371 National Stage Filing of International Application No. PCT/KR05/01066, filed 13 April 2005, which claims priority under 35 U.S.C. 119(a-d) to Korean Application No. 10-2004-0025217, filed 13 April 2004.

Specification

Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary.

The abstract of the disclosure is objected to because: a) it neither provides for the general nature of the compound(s) nor exemplifies any members or formulae illustrative of its class. Correction is required. See MPEP § 608.01(b). It suggested that Applicant amend the abstract to include a depiction of formula (I).

Claim Objections

Claim 5 is objected to because of the following informalities:

Claim 5 recites the limited of a process "which comprises step of". It is suggested that Applicant amend the claim to correct this grammatical error. Appropriate correction is required.

Claim 10 recites the step of "subjecting a compound of formula (XVII) to bromination obtain a compound…". It is suggested that Applicant amend the claim to correct this grammatical error. Appropriate correction is required.

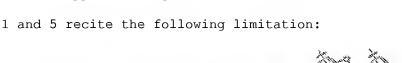
Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 5 recite the following limitation:



From this language, the meters and bounds of the substituents on R_3 are unclear. Specifically, it is unclear whether the C_{1-6} alkyl and C_{3-6} cycloalkyl groups may be substituted with the groups listed at the end of limitation. It is suggested that:

(1) if these groups may be substituted, Applicant should state that "R_3 may be unsubstituted or substituted with one or more substituents selected from the group consisting of...", or

(2) if these groups may not be substituted, Applicant should state specifically which moieties may be substituted with one or more substituents selected from the group.

Similar issues exist for the definitions of R^a (in claims 1, 5), R^e (in claim 1, 5), R_3 (in claim 2), R^e (in claim 2), R_3 (in claim 3). It is suggested that Applicant clearly indicated which members of the limitations may be further substituted.

Claim 4 recites the limitation "6-(2-adaman-1-ylethoxy)-1-(*trans*-methylimino-*N*-oxy)-3-phenyl-1H-indene-2-carboxylate ethyl ester" as species number 24. There is insufficient antecedent basis for this limitation in the claim. Specifically, Claim 1 does not provide for R^e to be adamantyl. It is suggested that Applicant amend Claim 1 to provide for R^e to be adamantyl.

Claim 4 recites the limitation "1-(*trans*-methylimino-*N*-oxy)-3-phenyl-6-(pyridine-2-yloxy)-1H-indene-2-carboxylate ethyl ester" as species number 90. There is insufficient antecedent basis for this limitation in the claim. Specifically, Claim 1 does not provide for R_6 to be pyridine-2-yloxy. It is suggested that Applicant amend Claim 1 to provide for R_6 to be pyridine-2-yloxy.

Claims 5-11 recite the step of "subjecting indenone compound of formula (II) to a condensation reaction with R^1NHOH or NH^2OH to obtain a compound of formula (III), and reacting the compound of formula (III) with R_3X." It is unclear how subjecting the indenone compound of formula (II) to a condensation reaction with R_1NHOH can lead to the compounds of formula (III). It is suggested that Applicant amend the claim to clearly indicate that two

distinct processes can be used to convert the compound of formula (II) to the compound of formula (I).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

NOTE: Applicant is claiming compositions in claims 12 and 13; however, Applicant has recited an intended use for these compositions. As per MPEP 2111.03:

> During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. If so, the recitation serves to limit the claim. See, e.g., *In re Otto*, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963).

Examiner has determined that since Applicant has claimed compositions that comprise "a therapeutically effective amount of the compound or salt defined in claim 1 as an active ingredient," the term "therapeutically" results in a structural difference. In particular, in order to make and use the invention, a person having ordinary skill in the art would need determine what constitutes a therapeutically effective amount with respect to the intended use. Accordingly, the

following analysis demonstrates that undue experimentation is needed in order to make and use the compositions claimed.

Claims 12 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition for the treatment of diabetes, obesity, arterisclerosis, hyperlipidemia, hyperinsulinisim, hypertension, osteoporosis, liver cirrhosis, or asthma, does not reasonably provide enablement for a pharmaceutical composition for modulating the activities of PPARs, the prevention of the diseases recited, or the treatment of cancer, in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The relevant factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph have been set forth in *In re* Wands. See *In re* Wands, 8 USPQ.2d 1400 (1988). The factors are as follows:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention is drawn to pharmaceutical compositions comprising a therapeutically effective amount of the compound or salt defined in claim 1 that are intended for use in modulating the activities of PPARs, and treating and preventing the diseases listed in claim 13.

The State of the Prior Art and the Predictability or Lack Thereof in the Art

A full analysis will not be provided for the numerous diseases listed; however, the following examples demonstrate that the broad usage in claim 12 and the specific uses in claim 13 are unpredictable.

The state of the art with respect to the modulation of PPARs is that the treatment of diseases with a connection to the activity of PPAR activity remains highly unpredictable. Shearer and Billin (*Biochimica et Biophysica Acta* **2007**, *1771*, 1082-1093) teach that three distinct PPAR subtypes have been identified and that while these subtypes have a high level of sequence homology, "each has distinct physiological functions." (See page 1082, Section 1) Furthermore, Shearer and Billin further discuss compounds that have been discovered to modulate one specific subtype over the other, producing effects characteristic to the function of the subtype. Moreover, Shearer and Billin provide the state of the art by stating that "The ability of each PPAR subtype to regulate distinct metabolic pathway has led to the investigation of combination approaches. The ultimate goal of the combination agonist strategy is to activate each receptor subtype to provide maximal efficacy on appropriate target genes associated with specific pharmacological pathways while minimizing adverse side effects." While Shearer and Billin describe the idealized model of potential PPAR modulators, the relative

effects of a single molecule at three separate receptors renders the pursuit challenging and unpredictable. (See page 1085, Section 4)

The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known (see Golub et al., Science, Vol. 286, October 15, 1999, pages 531-537) that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, to maximize efficacy and minimize toxicity. Cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al., Science, Vol. 286, October 15, 1999, pages 531-537). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

In the instant case, Applicant discloses an assay for determining the level of PPAR$_\gamma$ activation on page 67 of the specification as well as an in vivo (mouse) to determine effectiveness if lowering blood glucose level on page 69.

The specification fails to bridge the gap between the compounds effects in a patient suffering from the divergent diseases connected to PPAR regulation and PPAR modulators that have indications in various divergent

etiologies, causes and effects. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that compositions which fall within the scope of a claim will posses the alleged activity.

The Quantity of Experimentation Needed

The nature of the pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds or compositions exhibit the desired pharmacological activities for each of the diseases instantly claimed in the methods of use. The quantity of experimentation needed would be undue when faced with the lack of testing and when faced with the unpredictability of the pharmaceutical art. Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability," etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

Furthermore, with respect to the fact that Applicant is claiming uses for the prevention of various diseases, pharmacological prevention of a disease requires a vast amount of experimentation. A person having ordinary skill in the art would need to determine factors that make a certain subject prone to developing a disease, administer a pharmacological agent over a long period of time to ensure true prevention, perform background experiments, etc. Hussain et al. have discussed the possible experimental burden for the disease diabetes (Diabetes Research and Clinical Practice 2007, 76, 317-326. Specifically, Hussain et al. teach that "it is unlikely that a study would ever be undertaken to demonstrate an impact of upstream intervention on the incidence of diabetes or cardiovascular outcomes. It is difficult in the sense of logistics, economy and ethical dilemma in replicating randomised

controlled trials in the general population over a prolonged period of time." A person having ordinary skill in the art at the time the invention was made would be faced with an undue amount of experimentation to use the pharmaceutical compositions for the claimed intended uses.

The Level of the Skill in the Art

Even though the level of skill in the pharmaceutical art is very high, based on the unpredictable nature of the invention and state of the prior art, one skilled in the art could not use the claimed invention without undue experimentation.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. {*In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)}.

The determination that *undue experimentation* would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. (*In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404). These factual considerations are discussed comprehensively in MPEP § 2164.08 (scope or breadth of the claims), § 2164.05(a) (nature of the invention and state of the prior art), § 2164.05(b) (level of one of ordinary skill), § 2164.03 (level of predictability in the art and amount of direction provided by the inventor), § 2164.02 (the existence of working examples) and

§ 2164.06 (quantity of experimentation needed to make or use the invention based on the content of the disclosure).

Based on a preponderance of the evidence presented herein, the conclusion that applicant is insufficiently enabled for making and using a pharmaceutical composition for modulating the activities of PPARs, the prevention of the diseases recited, or the treatment of cancer, in general, is clearly justified.

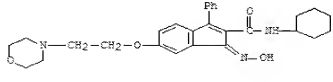
Closest Prior Art

The compound closest in structure to the instantly claimed genus is the following structure taught by Mugnier et al. (J. Org. Chem. 1993, 58, 5329-5334):

.

The prior art compound above does not read on Applicant's broadest claim nor does the prior art provide a motivation to arrive at a compound instantly claimed via modification of the above structure.

Furthermore, the following structure, taught by Cheon et al. in U.S. Patent Application Publication No. 2007/0225288 A1, is of analogous structure:



.

It is noted that the above compound is only taught as an intermediate *en route* to structurally distinct compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew P. Coughlin whose telephone number is (571)270-1311. The examiner can normally be reached on Monday through Thursday from 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JAMES O. WILSON can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Matthew P. Coughlin/ **/James O. Wilson/**
Examiner, Art Unit 4131 **Supervisory Patent Examiner, Art Unit 1624**